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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,807	07/29/2002	James Duncan Morrison	9013-46	2452

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EXAMINER	
AUDET, MAURY A	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,807	MORRISON ET AL.	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,24-34 and 37-42* is/are pending in the application.

4a) Of the above claim(s) *1,3-23,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,24-34 and 37-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Applicant's response and arguments filed 10/1/03 are acknowledged. Claims 2, 24-34, and 37-42 are pending (as drawn to elected peptide insulin), and claims 1, 3-23, and 35-36 remain withdrawn from consideration (but have not yet been cancelled).

Due to the new rejections below, and prior art references cited therein, this action is made NON-FINAL.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). Although the present case is a 35 U.S.C. § 371 application and reference is made to the abstract of the WO 01/09163 A3 (PCT/GB00/02903), a new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

35 U.S.C. § 112, 1st ¶, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an

enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

The claimed invention, is drawn to the elected insulin-bile acid conjugates, among the many other species compounds that may be conjugated to bile acids, as well as "analogues and fragments of all these", including insulin.

One of skill in the art would not recognize from the disclosure that the Applicant was in possession of the claimed "analogues and fragments" of insulin or any of the other compounds of claim 33. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116). Namely, although the specification describes the formal structure (by name) of all the compounds of claim 33, it does not describe any of the "analogues and fragments of all these".

Thus, neither the claims nor the specification details the "analogues and fragments of all these" compounds, including elected species insulin. One of skill in the art would not recognize from the disclosure that the Applicant was in possession of the genus, namely all the "analogues and fragments of all these".

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

35 U.S.C. § 112, 1st ¶ Scope of Enablement

Claims 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific compounds of claim 33, including elected species insulin, does not reasonably provide enablement for the "analogues and fragments of all these". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for "analogues and fragments of all these" compounds, including elected species insulin, for the following reasons:

The nature of the invention: The claimed invention is drawn to the elected insulin-bile acid conjugates, among the many other species compounds that may be conjugated to bile acids, as well as "analogues and fragments of all these", including insulin.

The state of the prior art and the predictability or lack thereof in the art:

> Isolation, purification, formulation, and delivery of proteins represent significant challenges to pharmaceutical scientists, as proteins possess unique chemical and physical properties. These properties pose difficult stability problems (Abstract). With the recent advances in recombinant DNA technology, the commercial production of proteins for pharmaceutical purposes has become feasible. [] Unfortunately, proteins possess chemical and physical properties which present unique difficulties in the purification, separation, storage, and delivery of these materials. (Manning et al., Pharmaceutical Research, p. 903).
>
> Single amino acid substitution can alter antigen-binding specificity (Rudikoff et al., Immunology. Vol. 79, March 1982: 1979-83).

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification describes the formal structure (by name) of all the compounds of claim 33, but does not describe any of the "analogues and fragments of all these".

The breadth of the claims and the quantity of experimentation needed: The claims (33-34) are drawn broadly to the "analogues and fragments of all these" compounds, including elected species insulin. Absent sufficient teachings in the specification or art sufficient to overcome the teachings of unpredictability in the art as to enablement of the "analogues and fragments of all these" compounds, including elected species insulin, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-29, 32-33, 37, and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-29, 32-33, 37, and 39-40 recites the limitation "The pharmaceutical composition" in the above claims. These claims depend from claim 2, namely a "compound" [an amide of a bile acid/slat of formula (II)]. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 is unclear because the invention is drawn to bile acid-peptide conjugate compositions, but one of the "peptides" claimed is "polysaccharide" (claim 33, line 13). A polysaccharide is a sugar, not a peptide. Although the claims have only been examined based on the elected species insulin, at the present time (since art reading on species has been found and applied), the inclusion of "polysaccharide" amongst the peptide species is nevertheless improper as not being drawn to the invention. It is suggested that the term "polysaccharide" be cancelled.

In claims 33-34 it is unclear what is contemplated as the "analogues and fragments" of elected species insulin (or any of the other agents listed). The specification has only described

the formal structure (by name) of all the compounds of claim 33. It is suggested that "analogues and fragments of all of these" be cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 24-34, and 37-42 rejected under 35 U.S.C. 103(a) as being unpatentable over Byun et al. (US 6245753) in view of Kramer et al. (J Biol. Chem. 1992 Sep 15;267(26):18598-604) and Longenecker et al. (US 4994439).

Byun et al. teach the conjugation of polysaccharides (such as heparin) to any bile acid at the free carboxyl group [C-24] and uses thereof (col. 4, lines 34-36; col. 6, lines 1-4, 18-20, and 23-25), for enhanced oral administration (Ex. 7), and intestinal absorption (col. 6, lines 11-20). Byun et al. does not expressly teach the conjugation to bile salts of other active agents (i.e. other than polysaccharides) lacking effective absorption after oral administration due to size; in order to enhance absorption of the active agent, i.e. peptides, such as insulin.

Kramer et al. teach the conjugation of peptides at the C-24 location of bile acid compounds; [f]or example, peptide-drugs like the oxaprolylpeptide inhibitors of prolyl-4-hydroxylase, are not transported in intact form from the blood into the bile in contrast to the respective bile acid conjugates" . . . (abstract, "Discussion" column 1, last s., and entire

document) [for the] "improvement of intestinal absorption of nonabsorbable drugs by covalent linkage of the respective drugs to bile acids" (last sentence of "Discussion", and entire section).

Longenecker et al. teach that *"[i]t is by now well known that bile salts are capable of enhancing the absorption of peptides, such as insulin and other drugs*, across the nasal mucous membrane and across the rectal and vaginal mucous membranes (Duchateau, G.S.M.J.E. et al, in "Studies on Nasal Drug Delivery" (1986) Thesis:University of Amsterdam, pp. 87-98, citing Collens, W.S. et al, Proc Soc Exp Biol & Med (1932) 29:756-758; Toultou, E., et al, J Pharm Pharmacol (1978) 30:662-663 and a variety of other references).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate insulin at the C-24 carboxyl group of any bile acid in the polysaccharide-bile acid conjugates (conjugated at the free C-24 carboxyl group of bile acids) of Byun et al., because Kramer et al. teach the advantageous conjugation of peptides [which insulin is classified as] to the C-24 carboxyl group of bile acids for enhanced intestinal absorption and Longenecker et al. teach that it is advantageously well known to use insulin with bile acids for enhanced absorption. Furthermore, because Byun et al. teach the advantageous conjugation of polysaccharides to bile acids at the free carboxyl group (C-24); which Applicant too has expressly included (polysaccharides), among the myriad of peptides (or more aptly larger "pharmaceutical agents", since enzymes and hormones are included therein also), as one of the key pharmaceutical agents which may benefit through absorption assistance by conjugation to bile acids.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
December 29, 2003

HERBERT J. LILLING
PATENT EXAMINER
GROUP 1600 ART UNIT 1651